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APPL. NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
SCHWADRON,R

18M2/0714

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ART UNIT	PAPER NUMBER
1806	12

DATE MAILED: 07/14/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 5/5/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9, 11-16, 18, 19 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-9, 11-16, 18, 19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 1-9,11-16,18,19 are under consideration. Claims 1,8,14,18,19 have been amended. Claims 18,19 are newly added.

RESPONSE TO APPLICANT'S ARGUMENTS

16. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. Newly added claims 18,19 and claims 1-9,11-16 stand rejected under 35 U.S.C. § 101 for the reasons discussed in paragraph 17 of the previous Office Action. Applicant's arguments have been fully considered but they are not deemed persuasive. Applicant has still provided no evidence of the efficacy of the instant invention for the treatment of humans in vivo. Applicant has provided no evidence that the pig model data presented in the specification apriori establishes that the instant invention will work in humans. With regards to Bowie et al., there is no evidence in said article that a pig model for antibody mediated therapy demonstrates that said therapy would work in humans. With regards to Chesebro et al., there is no evidence in said article that a pig model for antibody mediated therapy demonstrates that said therapy would work in humans. With regards to Fass et al., there is no evidence in said article that a pig model for antibody mediated therapy demonstrates that said therapy would work in humans. With regards to the Fuster et al. papers, there is no evidence in either article that a pig model for antibody mediated therapy demonstrates that said therapy would work in humans. With regards to Griggs et al., there is no evidence in said article that a pig model for antibody mediated therapy demonstrates that said therapy would work in humans. With regards to Montagna et al., the following quotes suggest that pig skin is not an appropriate model for human skin:

"This study makes it clear that in spite of a few similarities, the dissimilarities in morphologic and histochemical attributes of the skin of the pig and that of man are considerable. In light of this, we should all reflect soberly in the future before uttering again the fantasy that the skin of the pig resembles more that of man than that of any other mammal. To seek a skin similar to that of man, consideration should be given to the anthropoid primates, and particularly, the apes." (page 20, second column, last paragraph).

With respect to applicant's print out listing 1308 titles, Examiner has found no evidence that demonstrates the efficacy of murine

antibodies for the treatment of human disease. With regards to CENTOXIN, not only has this antibody not been approved by the FDA for human use, in clinical trials said antibody showed no greater efficacy for the treatment of sepsis than placebo (see Rhein, page 1, second column, first paragraph). With regards to OKT3, Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. "(see page 1657, first column, last paragraph). The fact that only one murine antibody has been approved for clinical use in view of widespread attempts to use antibodies therapeutically, confirms the comments expressed by Harris et al. The Taylor et al. papers provide no evidence of the efficacy of the instant invention for the treatment of human disease.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to for the reasons discussed in the previous Office Action in paragraph 17, sections A and B.

19. Newly added claims 18,19 and claims 1-9,11-16 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification. Applicant's arguments have been considered and deemed not persuasive. With regards to section A, the claims remain rejected for the reasons elucidated in paragraph 19 of the previous Office Action and paragraph 17 of the instant Office Action. With regards to section B, applicants arguments have not been found persuasive. Applicant has provided no evidence that inhibitors of a natural anticoagulant other than antiprotein c antibodies will reduce microvascular bleeding. The fact that antibodies against protein s will inhibit one function of protein s in a totally unrelated assay does not apriori establish that antiprotein s antibodies will work in the instant invention. No evidence has been provided with regards to the other listed compounds and their ability to work in the instant invention.

20. Newly added claims 18,19 and claims 1-9,11-16 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited for the reasons detailed in paragraph 21 of the previous Office Action. Applicant's arguments have been considered and deemed not persuasive. The rejection stands for essentially the same reasons as elaborated in paragraphs 17 of the instant Office Action.

21. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to for the reasons discussed in the previous Office Action in paragraph 25.

22. Claim 4 remains rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification. Applicant's arguments have been considered and deemed not persuasive. Applicant has not addressed the issues raised in said rejection.

23. Newly added claims 18,19 and claims 1-9,11-16 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited for the reasons detailed in paragraph 27 of the previous Office Action. Applicant's arguments have been considered and deemed not persuasive. Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody has unique properties which distinguish it from other antiprotein C antibodies, including $CA^{2}+$ dependency (see columns 2). It is not apparent that any antibody per se against protein C would be able to mediate the microvascular bleeding inhibition effect achieved when this antibody with unique properties is used. In addition it is equally unclear whether non antibody agents that inhibit protein C function would be able to mediate the effect seen using the HPC-4 antibody.
Applicant has presented no evidence of the use of any agent or antibody other than HPC-4 in the specification of the instant invention.

24. Newly added claims 18,19 and claims 1-9,11-16 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited for the reasons detailed in paragraph 27 of the previous Office Action. Applicant's arguments have been considered and deemed not persuasive. Applicant has provided no evidence as to the efficacy of the instant antibody in treating microvascular bleeding when the antibody is administered after microvascular bleeding has occurred.

25. The rejection of claims 1-9,11-16 under 35 U.S.C. § 112, second paragraph is withdrawn in view of the amended claims.

26. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

27. Newly added claim 18 and claims 1-4,7,11-13 stand rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) in view of Esmon et al (US Patent 5,147,638) for the reasons elaborated in paragraph 30 of the previous Office Action. Applicant's arguments have been considered and deemed not persuasive. Esmon et al (US Patent 5,202,253) teaches the antiprotein c antibody of the instant invention(see entire document). Esmon et al. (US Patent 5,202,253) teaches that the antiprotein C antibody can be used to promote clotting (see paragraph four, column 12). It would have been obvious to a routineer that this statement referred to clotting at any anatomical site or location and was applicable to normal tissue. Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed (see paragraph three, column 13 and Esmon et al (US Patent 5,147,638)). It would have been obvious to a routineer that microvascular bleeding in any anatomical location or site could be stopped by treatment with antiprotein c antibody. It would have been obvious to a routineer that said antibody could be delivered by any art recognized mode of administration.

28. Newly added claim 19 and Claims 5,6,8,9,14-16 stand rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) in view of Esmon et al (US Patent 5,147,638) and

further in view of Suzuki et al. for the reasons elaborated in paragraph 31 of the previous Office Action. Applicant's arguments have been considered and deemed not persuasive. Applicant's arguments deal with issues addressed in paragraph 27 of the instant rejection. It would have been obvious to a routineer that both the coagulant and the antiprotein c inhibitor could have been administered topically, because topical administration is an art known mode of administering therapeutic agents which work locally.

29. No claim is allowed.

30. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

30. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

R Schwadron

Ron Schwadron, Ph.D.
July 13, 1994

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
7/14/94